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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/848,852	05/04/2001	Jennifer L. Hillman	PF-0515-1 CON	8542

27904 7590 12/31/2002

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/848,852	Applicant(s) Hillman et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 1, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 9-16, 28, 29, and 46-49* is/are pending in the application.

4a) Of the above, claim(s) *1, 2, 11, 14-16, 28, 29, and 46-48* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3-7, 9, 10, 12, 13, and 49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1.5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed November 1, 2002 (Paper No. 6) in response to the Office Action of October 1, 2002 (Paper No. 5) is acknowledged and has been entered. Examiner appreciates the information drawn to the cancellation of claims in the Transmittal filed May 4, 2001. Claims 8, 17-27, 30-45 are hereby canceled. Examiner apologizes for any inconvenience occasioned by the inadvertent restriction of the canceled claims. Claims 1-7, 9-16, 28-29, 46-49 are pending in the application. Claims 1-2, 11, 14-16, 28-29, 46-48 and all subject matter drawn to examination of polynucleotides encoding SEQ ID NO:1 or polynucleotides of SEQ ID NO: 2 recited in the elected claims have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions Claims 3-7, 9-10, 12-13 and 49 are pending in the application and are currently under prosecution.

2. Applicant points out that Examiner has mischaracterized the limitations of claim 29 in Paper No. 5. A review of the claim reveals that Applicant is correct. Examiner acknowledges that claim 29 is drawn to a method of assessing toxicity of a test compound. Examiner apologizes for any inconvenience.

3. Applicant's election with traverse of Group 4, SEQ ID NO:4, encoding SEQ ID NO:3 claims 3-7, 9-10, 12-13 and 49 in Paper No 6 is acknowledged. The traversal is on the ground(s) that Groups 1-4 could be examined at the same time without undue burden on the examiner. This is not persuasive. The literature search, particularly relevant in this art, is not coextensive different searches and issues are involved in the examination of each group. Further, the traversal is on the ground(s) that (a) the restriction although drawn to separate Groups is more

properly drawn to separate species as the claims are written in Markush format, (b) the Practice Re Markush-Type Claims broadly states that unity of invention exists where compounds included within a Markush Group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility, (c) the members of the Markush group are sufficiently few in number and so closely related that a search and examination of the entire claim can be made without serious burden, even if directed to independent and distinct inventions, (d) it is improper for the office to refuse to examine that which applicants regard as their invention unless the subject matter in the claims lack unity of invention, (e) MPEP states that 10 sequences will generally not be subject to a restriction requirement.

The arguments have been considered but have not been found persuasive because (a') and (b') the specification presents no data suggesting that the claimed sequences share a common utility as no specific utility has been ascribed to either claimed sequence, as will be more fully discussed below drawn to the utility of SEQ ID NO:4 under 35 USC 101. Further, the two sequences do not appear to share substantial structural features that are essential to any utility as pages 16-17 clearly demonstrate the differences between the proteins encoded by the two sequences, for example, the two sequences encode polypeptides with different numbers of amino acids, potential glycosylation sites in different domains of the encoded proteins, different numbers of potential casein kinase II phosphorylation sites, different numbers of potential PKC phosphorylation sites, PAWES-1 shows similarity to protein fingerprints derived from regions of prostaglandin/thromboxane receptors and PAWES-2 shows similarity to a Type I EGF motif signature, thus it would be

expected that the polynucleotides encoding these proteins would be correspondingly different and have no substantial structural features that are essential to a utility, (c') due to the complex nature of the invention, search of the entire claim can not be made without serious burden, (d') the claims as written are not in correct proper Markush format as the claimed sequences do not appear to have unity of invention for the reasons set forth above, (e') the MPEP specifically states that "**up to** ten independent and distinct nucleotide sequences will be examined in a single application without restriction". Due to the complex nature of the claimed material, search of the addition sequence is an undue burden.

Applicant further traverses the restriction of claims 14-16, 28-29 drawn to a method of using the polynucleotides and argues that the inventions should be examined together in light of *In re Ochiai.* This is not persuasive as the scope of the method claims is not the same as the claimed product inventions.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Objections

4. Claims 3-4 and all claims dependent thereon are objected to because claims 3-4 are dependent upon nonelected claims 1 and 2. The rejection can be obviated by amending claims 3-4 to include the limitations of claims 1 and 2, respectively.

5. All of the claims are objected to because they recite limitations drawn to non-elected inventions. Applicant is required to amend the claims to remove these limitations.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

7. Claims 3-7, 9-10, 12-13, 49 are rejected under 35 USC 101 because the claimed invention is not supported by a specific asserted utility, a substantial utility, or a well established utility.

The disclosed utilities for the polynucleotides, polynucleotides encoding polypeptides and naturally occurring variants thereof, encoding fragments thereof, methods of producing said polypeptides, naturally occurring variants thereof, complements thereof, include *in vivo* and *ex vivo* therapy, diagnosis and prevention of cell proliferative disorders, monitoring patients treated with agonists, antagonists or inhibitors of the encoded proteins, use of the polynucleotides as hybridization probes for the detection of related sequences, for mapping naturally occurring genomic sequences, as a target in a microarray which is then used for large scale correlation studies or functional analysis of sequences mutations, variants or polymorphisms and the expression of the polypeptide encoded by the polynucleotides. However, neither the specification nor any art of record teaches what the polynucleotides are, what they do, they do not teach a utility for any of the encoded polypeptides or fragments thereof, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for the polynucleotides, such as genome mapping,

hybridization probe and microarray constituent apply to many unrelated polynucleotide sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to the polynucleotides claimed, especially in light of the failure to disclose any particular relationship of what is claimed to any particular chromosome, cell type, etc. The asserted utility of the claimed polynucleotide appears to be based on the assertion that the polynucleotide encodes a polypeptide wherein the region of PAWES-2 (SEQ ID NO. 3), N285-H300 is similar to a Type I EGF motif signature and contains two cysteine residues characteristic of this motif and that the encoded polypeptide has a unique sequence from about amino acid 50 to about amino acid 59. Further, northern analysis has shown expression of this sequence in various cDNA libraries associated with cancer or immune response, and it is found in some reproductive tissue, cardiovascular tissue and gastrointestinal tissue cDNA libraries. However, it is noted that the only specific information about PAWES-2, other than the sequence is that it has a region similar to a Type I EGF motif signature and a unique region. There is no indication that the Type I EGF motif signature is the consensus sequence for any particular function. There is no indication of the amount of homology of N285-H300 to the putative motif signature. Further, the polypeptide encoded by the claimed polynucleotide has 332 amino acids. The putative similar signature (with undefined similarity other than the two cited cysteines that are characteristic of this motif) comprises 16 of those amino acids which is 5% of the encoded polypeptide. The specification does not state that the claimed polynucleotide encodes a Type I EGF proein or that the encoded polypeptide has any homology to a Type I EGF protein,

thus, the claimed invention does not have a well-established utility. As drawn to the "similar" signature with only two similar amino acid residues identified, it is well known in the art that even a single amino acid change will change the structure and the function of a protein. Bowie et al (Science, 1990, 257:1306-1310, IDS item) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990, IDS item) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252, IDS item) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or

asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein and with only two identified amino acid residues it cannot be predicted, nor would it be expected, that the "similar" Type I EGF domain would function as an Type I EGF domain. Finally, even if the claimed polynucleotide encodes a Type-I EGF - like or related polypeptide, neither the specification nor any art of record teaches what the invention is, what it does, does not teach a relationship to any specific disease or establish any involvement of the invention in the etiology of any specific disease or teach which variants might be active or would function as claimed Given only a similarity to a signature, the function of the encoded polypeptide and the claimed polynucleotide could not be predicted, nor would it be expected to be the same as that of Type I EGF. In order to determine a "real world use" of the claimed polynucleotide, further experimentation would be required, thus the invention does not have substantial utility. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility, a substantial utility, a well-established utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

9. Claims 3-7, 9-10, 12-13 and 49 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

10. If Applicant were able to overcome the rejections under 35 USC 101 and 35 USC 112, first paragraph above, Claims 3-7, 9-10 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising SEQ ID NO:4, does not reasonably provide enablement for a polynucleotide encoding SEQ ID NO:3 or a method of making SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The claims are drawn to a polynucleotide encoding SEQ ID NO:3 and a method of making said polypeptide. The specification teaches that SEQ ID NO:3 is a putative peptide encoded by a consensus sequence, derived from overlapping and/or extended nucleic acid sequences (ESTS) (p. 14) and teaches conventional

methods of producing polypeptides (pgs 19-20). One cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching of whether any protein product is actually produced **in vivo.** Because SEQ ID NO:4 is simply a polynucleotide fragment, it is not possible to determining what the ATG start site of any protein might be and it cannot be determined if the sequence would be in-frame to encode any protein. It is well known in the art that the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M. Et al, 1995, Pediatric Res., 37(6):681-686). Further, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31 , pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al

(EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if SEQ ID NO:4 could in fact translated into a polypeptide expression product. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention

11. In the event that Applicants might be able to overcome the 35 USC 101 and 35 USC 112, first paragraph rejections above, Claims 3-4, 6-7, 9-10, 12-13 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising SEQ ID NO:4 and the complete complement thereof does not reasonably provide enablement for polynucleotides encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:3, encoding polypeptides having the amino sequence of SEQ ID NO:3, encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO 3 having biological or immunogenic activity, naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4 or fragments of SEQ ID NO:4. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted that, for examination purposes, the term "having" in claim 1, sections (c) and (d) is read as an open term, thus a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3 is read as a fragment of a polypeptide "comprising" SEQ ID NO:3 which clearly reads on fragments having no identity whatsoever with SEQ ID NO:3 since the fragments are not required to be from a polypeptide consisting of SEQ ID NO:3.

The claims are drawn to encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:3, encoding polypeptides having the amino sequence of SEQ ID NO:3, encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3, wherein the fragment is biologically active, encoding immunogenic fragments of SEQ ID NO:3, fragments encoding naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4. Because the polynucleotide variants and the polypeptides encoded thereby are not defined in the specification, they can be read to encompass both conservative and nonconservative alterations which would encode proteins that would have either conservative or nonconservative alterations. Further, the broadly written claims encompass polynucleotides that comprise fragments of SEQ ID NO:4 from one to any number of nucleotide residues. One cannot extrapolate the teaching of the specification to the scope of the claims because the specification has not shown that variant

polynucleotides or polynucleotides encoding polypeptides produced by variants of polynucleotides encoding SEQ ID NO:3 or polynucleotides comprising fragments of SEQ ID NO:4 are capable of functioning as that which is suggested. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use the polynucleotides that encode the broadly claimed polypeptides for the reasons disclosed above drawn to the Bowie et al, Lazar et al, and Burgess et al references. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Further, as drawn to the "immunogenic fragment", it would not be possible to determine with any predictability whether, for example, the antibodies produced from the claimed immunogenic fragment that could be derived from SEQ ID NO:3 will actually bind to SEQ ID NO: 3. Roitt et al, 1998, Immunology, 4th ed, Mosby, London teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with peptides which in each case generated high anti-

peptide specific immunoreactivities, however, none of the antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Furthermore, the claim does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which fragment or part of the SEQ ID NO:3 could be used to produce antibodies which will bind specifically to SEQ ID NO:3. Further as drawn to claim 1, sections (c) and (d), the claims as written are drawn to encoded fragments with no identity to SEQ ID NO:3 because they are drawn to fragments of a polypeptide which comprises SEQ ID NO:1. The rejection drawn to the "having" language can be overcome, for example, by amending the cited segments to delete the term "having" and substituting the phrase "consisting of".

As drawn to the claimed "complements", the specification teaches that the term complementary refers to the natural binding of polynucleotides under permissive salt and temperature conditions and specifically teaches that complementarity between two single-stranded molecules may be "partial" or it may be "complete" (p.9, lines 7-16).. Complementary polynucleotides, as disclosed by the specification, include not only the complement, which is completely complementary to the claimed polynucleotides encoding SEQ ID NO:3 but also,

because the term "partial" is unlimited and undefined, includes a substantial number of species which lack significant complementarity to the claimed polynucleotides. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims **would not** share either structural or functional properties with polynucleotides that encode SEQ ID NO:3 or encode proteins that share either structural or functional properties with SEQ ID NO:3.

The specification fails to provide an enabling disclosure for how one would use the broadly claimed polynucleotides. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed invention. For the above reasons, undue experimentation would be required to practice the claimed invention.

12. Claims 3-4, 6-7, 9-10, 12-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:4 and the complete complement thereof and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acid sequences at least 90% identical to the amino acid sequence of

SEQ ID NO:3, encoding polypeptides having the amino sequence of SEQ ID NO:3, encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:3, wherein the fragment has biological activity, encoding immunogenic fragments of SEQ ID NO:3, naturally occurring polynucleotides having at least 90% identity to SEQ ID NO:4, polynucleotides complementary to SEQ ID NO:4 or said naturally occurring polynucleotide with at least 90% identity to SEQ ID NO:4.

It is noted that, for examination purposes, the "naturally occurring" sequences are understood to be drawn to allelic variants of the claimed sequence.

The specification discloses an isolated cDNA sequence, SEQ ID NO: 4, which encodes a predictive polypeptide sequence, SEQ ID NO:3. Absent evidence to the contrary, the sequence elected for examination is deemed to be an incomplete cDNA. Because the cDNA that corresponds to the SEQ ID NO mentioned in the claim is not full-length, a sequence prepared from undefined parts of a cDNA clone will not comprise the entire coding region of any particular gene, nor is it clear the partial sequence is even in frame to encode a polypeptide. The claims, as written, however, encompass polynucleotides which vary substantially in length and also in nucleotide composition.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a

substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using... There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore

not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, comprising SEQ ID NO: 4 or fragments thereof.

Further, as drawn to the naturally occurring variant sequences, as disclosed above, these are read as allelic variants of the claimed sequence. Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlag, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:4, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a specific nucleotide sequences, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

13. Claims 12, 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12, and dependent claims 13 are indefinite because claim 12 recites the phrase "equivalent of". The phrase is confusing because it is not clear what is meant by an "equivalent". The term is a relative term which renders the claim indefinite. The term"equivalent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 3, 6, 7, 9, are rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 5,683,898.

The claims are drawn to an isolated polynucleotide encoding a polypeptide comprising an immunogenic fragment of SEQ ID NO:3.

US Patent No.5,683,898 teaches SEQ ID NO: 2 which encodes a polypeptide comprising multiple fragments of SEQ ID NO:3 (see Sequence Search data us-09-848-852-3.rni, result 2) as well as methods of making said polypeptide using vectors comprising promoter sequences by transformation of a host cell, see col 4 and Examples 2 and 3, col 8. Although the reference does not specifically teach that the encoded fragments are immunogenic, the claimed polynucleotide appears to be the same as the prior art polynucleotide, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Further, the reference teaches the polynucleotide in a plasmid, transformed into a host cell (cols 17 and 18) wherein the encoded polypeptide was expressed (col 19). All of the limitations of the claims are met.

16. Claim 12 ise rejected under 35 U.S.C. § 102(b) as being anticipated by as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93).

The claims are drawn to a nucleic acid molecule which is complementary to SEQ ID NO:4

The Boehringer Mannheim teaches random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924), and therefore a subset of the random primers would include the complement of the. Claimed polynucleotides All of the limitations of the claims are met.

17. No claims allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
December 16, 2002

```
;  INFORMATION FOR SEQ ID NO:  58:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  4835 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
US-08-976-259-58

Alignment Scores:
Pred. No.:                0.00929        Length:          4835
Score:                    108.00         Matches:         59
Percent Similarity:       31.69%         Conservative:    31
Best Local Similarity:    20.77%         Mismatches:      86
Query Match:              6.09%          Indels:          108
DB:                       4              Gaps:            11

US-09-848-852A-3 (1-332) x US-08-976-259-58 (1-4835)

Qy      42 LeuPheGlnGlySerAspLeuGlyMetAlaGluGluAlaGluArgProGlyGluLysAla 61
           ||||||     :::   |||||:::           |||:::|||
Db    1350 CTATTTTCCCTCGCTCGCCTAGGTATTGTGACGATGTTCGAACAACCGACTTTGGTGAAT 1409

Qy      62 GlyGlnHisSerProLeuArgGluGluHisVal------ThrCysValGlnSerIle--- 78
             :::                 ||||||:::      :::|||   :::   |||
Db    1410 CAAAAGCCACAATTACCTGCATATGAACATATTTTACGTAGCTGTCCCAGAGACATAGAC 1469

Qy      79 LeuAspGluPheLeuGlnThrTyrGlySerLeuIleProLeuSerThrAspGluValVal 98
           |||     |||:::              |||:::||||||   :::|||
Db    1470 CTGCTTGCATTTATAGATGCTGATGAATTTTTATTGCCACTTGAATCGGAT--------- 1520

Qy      99 GluLysLeuGluAspIlePheGlnGlnGluPheSerThrProSerArgLysGlyLeuVal 118
             |||   |||   |||   :::::|||         |||        :::
Db    1521 ACCAATTTGTCAGATTTTTTTTCTGAAAAGTTTCAGGATGAGAGTGTCAGCGCTATTGCA 1580

Qy     119 LeuGlnLeuIleGlnSerTyrGlnArgMetProGlyAsnAlaMetValArgGlyPheArg 138
           |||
Db    1581 TTG---------------------------------------------------------- 1583

Qy     139 ValAlaTyrLysArgHisValLeuThrMetAspAspLeuGlyThrLeuTyrGlyGlnAsn 158
                                                                    |||
Db    1584 ----------------------------------------------------------AAT 1586

Qy     159 TrpLeuAsn------------------------------------------------------ 161
           |||   |||
Db    1587 TGGGCAAATTTTGGTTCTAGTGGTGAATGGTTTGCTGAAGAGGGGTTGGTTATTGAACGT 1646

Qy     162 -----------AspGlnValMetAsnMetTyrGlyAspLeuValMetAspThrVal 176
                      |||     |||:::::   :::
 b     1647 TTTACCTATCGTGCCCCGCAATCCTTTAACGTTCATCATAACTTCAAAAGCGTGGTCAAA 1706

Qy     177 ProGluLysValHisPhePheAsnSerPhePheTyrAspLysLeuArgThrLysGlyTyr 196
           ||||||:::|||:::   |||::::::      |||      ||||||          |||
Db    1707 CCCGAACGAGTTAACCGCTTTCATAATCCGCATTATGCTGATTTGCGTTATGGTCGATAT 1766

Qy     197 AspGlyValLysArgTrpThrLysAsnValAspIlePheAsnLysGluLeuLeuLeuIle 216
                                   :::|||         ::::::|||:::|||
Db    1767 -------------------------ATCGATGCATTGGGTCGTGATTTGATTCTGCAC 1799

Qy     217 ProIleHis--------------LeuGluValHisTrpSerLeuIleSerValAspVal 231
           |||   |||                |||||   ||||||   :::   |||
Db    1800 CCGAGGCATGGTAATGGGGTTAGTGCTGAAGTGACTTGGAGCGGTGTCAGGGTA------ 1853

Qy     232 ArgArgArgThrIleThrTyrPheAspSerGlnArgThrLeuAsnArgArgCysProLys 251
                                                |||             |||
Db    1854 ----------------------------------------AATCACTATGCAGTTAAA 1871

Qy     252 His--------------IleAlaLysTyrLeuGlnAlaGluAlaValLysLysAspArg 266
                          :::   |||:::|||:::      |||         :::|||
Db    1872 TCACTTGAGGAATTCTTGTTGGGCAAGCATCTGCGTGGTAGTGCTGCCACTGCTAATCGA 1931

Qy     267 LeuAspPheHisGlnGlyTrpLysGlyTyrPheLysMetAsnValAlaArgGlnAsnAsn 286
           :::                 |||   |||||||||         |||         |||
Db    1932 GTAAAGCAT------------AAAGATTATTTCAAG---------GCACATGATCGTAAT 1970
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```
Qy     287 AspSerAspCys 290
           |||   :::|||
Db    1971 GATGAAGAGTGC 1982

RESULT 2
US-08-375-709-2
; Sequence 2, Application US/08375709
; Patent No. 5683898
;  GENERAL INFORMATION:
;    APPLICANT:  YAZAWA, Kazunaga
;    APPLICANT:  YAMADA, Akiko
;    APPLICANT:  KATO, Seishi
;    APPLICANT:  KONDO, Kiyosi
;    TITLE OF INVENTION:  Gene Coding For Eicosapentaenoic Acid
;    TITLE OF INVENTION:  Synthesizing Enzymes and Process for Production of
;    TITLE OF INVENTION:  Eicosapentaenoic Acid
;    NUMBER OF SEQUENCES:  19
;    CORRESPONDENCE ADDRESS: -
;      ADDRESSEE:  Foley & Lardner
;      STREET:  3000 K Street, N.W., Suite 500
;      CITY:  Washington
;      STATE:  D.C.
;      COUNTRY:  USA
;      ZIP:  20007-5109
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/375,709
;      FILING DATE:  20-JAN-1995
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/178,251
;      FILING DATE:  14-MAY-1993
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  JP 4-147945
;      FILING DATE:  15-MAY-1992
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  WEGNER, Harold C.
;      REGISTRATION NUMBER:  25,258
;      REFERENCE/DOCKET NUMBER:  53466/150/AAOK
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (202)672-5300
;      TELEFAX:  (202)672-5399
;      TELEX:  904136
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  1983 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  DNA (genomic)
;    ORIGINAL SOURCE:
;      ORGANISM:  Shewanella putrefaciens SCRC-2874 (FERM
;      ORGANISM:  BP-1625)
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..1983
;    FEATURE:
;      NAME/KEY:  mat_peptide
;      LOCATION:  1..1983
US-08-375-709-2

Alignment Scores:
Pred. No.:                0.169          Length:          1983
Score:                    93.00          Matches:         75
Percent Similarity:       32.96%         Conservative:    43
Best Local Similarity:    20.95%         Mismatches:      117
Query Match:              5.25%          Indels:          123
DB:                       1              Gaps:            19
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US-09-848-852A-3 (1-332) x US-08-375-709-2 (1-1983)

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Qy       9 GlyThrIleTrp-AlaArgArgGlyAlaHisLeuAlaProProAspAlaSerIleLeuIl 28
Db     537 GGACCACTTTGGCGGAGCTCGCGGTGTTCAAGAGATGTTCCCTGATGTCAAAGTCTACGG 596

Qy      28 eSerAsnValCysSerIleGlyAspHisValAlaGlnGluLeuPheGlnGlySerAspLe 48
Db     597 CTCA-----------------GATAACATCACTAAAGAAATTGTCGATGAGAACGTACT 638

Qy      48 uGly------------MetAlaGluGluAlaGluArgProGlyGluLysAlaGlyGlnHi 64
Db     639 TGCCGGTAACGCCATGAGCCGCCGCGCAGCTTATCAATACGGCGCAACACTGGGCAAACA 698

Qy      64 s----------------------------SerProLeuArgGluGluHisValThrCy 74
Db     699 TGACCACGGTATTGTTGATGCTGCGCTAGGTAAAGGTCTATCAAAAGGTGAAATCACTTA 758

Qy      74 sValGlnSerIleLeuAspGluPheLeuGlnThrTyrGlySerLeuIleProLeuSerTh 94
Db     759 CGTCGCCCCA------GACTACACCTTAAACAGTGAAGGCAAATGGGAAACGCTGACG-- 810

Qy      94 rAspGluValValGluLysLeuGluAspIlePheGlnGlnGluPheSerThr-------- 111
Db     811 ----------ATTGATGGTCTAGAGATGGTGTTTATGGATGCCTCGGGCACCGAAGCTGA 860

Qy     112 ----------------------ProSerArgLysGlyLeuValLeuGlnLeuIleGlnSe 124
Db     861 GTCAGAAATGATCACTTATATTCCCTCTAAAAAAGCGCTCTGGACGGCGGAGCTT---AC 917

Qy     124 rTyrGlnArgMetProGly---------------------------------------- 130
Db     918 CTATCAAGGTATGCACAACATTTATACGCTGCGCGGCGCTAAAGTACGTGATGCGCTCAA 977

Qy     131 ----------------AsnAlaMetValArgGlyPhe------------ArgValAlaTy 141
Db     978 GTGGTCAAAAGATATCAACGAAATGATCAATGCCTTTGGTCAAGATGTCGAAGTGCTGTT 1037

Qy     141 rLysArgHisVal-----------------------------------------LeuTh 147
Db    1038 TGCCTCGCACTCTGCGCCAGTGTGGGGTAACCAAGCGATCAACGATTTCTTACGCCTACA 1097

Qy     147 rMetAspAspLeuGlyThrLeuTyrGlyGln------AsnTrpLeuAsnAspGlnVal-- 164
Db    1098 GCGTGATAACTACGGCCTAGTGCACAATCAAACCTTGAGACTTGCCAACGATGGTGTCGG 1157

Qy     165 -MetAsnMetTyrGlyAspLeuValMetAspThrValProGluLysValHisPhePheAs 184
Db    1158 TATACAAGATATTGGCGATGCGATTCAAGACACGATTCCAGAGTCTATC----------- 1206

Qy     184 nSerPhePheTyrAspLysLeuArgThrLysGlyTyrAspGlyValLysArgTrpThrLy 204
Db    1207 ----------TACAAGACGTGGCATACCAATGGTTACCACGGCACT------TATAGCCA 1250

Qy     204 sAsnValAsp---IlePheAsnLysGluLeuLeuLeuIleProIleHisLeuGluValHi 223
Db    1251 TAACGCTAAAGCGGTTTATAACAAGTATCTA---------------------------- 1281

Qy     223 sTrpSerLeuIleSerValAspValArgArgArgThrIleThrTyrPheAspSerGlnAr 243
Db    1282 -------------------------------------GGCTACTTCGATATGAACCC 1301

Qy     243 gThrLeuAsnArgArgCysPro------LysHisIleAlaLysTyrLeuGln-------- 258
Db    1302 AGCCAACCTTAATCCGCTGCCAACCAAGCAAGAATCTGCCAAGTTTGTCGAATACATGGG 1361

Qy     259 -------AlaGluAlaValLysLysAspArgLeuAspPheHisGlnGlyTrpLysGlyTy 276
Db    1362 CGGCGCAGATGCCGCAATTAAGCGCGCTAAAGATGATTACGCTCAAGGTGAATACCGCTT 1421

Qy     276 rPhe--------------LysMetAsnValAlaArgGlnAsnAsnAspSer 288
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Db    1422 TGTTGCAACGGCATTAAATAAGGTGGTGATGGCCGAGCCAGAAAATGACTCC 1473

RESULT 3
US-08-752-929-2
; Sequence 2, Application US/08752929
; Patent No. 5798259
;  GENERAL INFORMATION:
;    APPLICANT:  YAZAWA, Kazunaga
;    APPLICANT:  YAMADA, Akiko
;    APPLICANT:  KATO, Seishi
;    APPLICANT:  KONDO, Kiyosi
;    TITLE OF INVENTION:  Gene Coding for Eicosapentaenoic Acid Synthesizing
;    TITLE OF INVENTION:  Enzymes and Process for Production of Eiscosapentaenoic
;    TITLE OF INVENTION:  Acid
;    NUMBER OF SEQUENCES:  25
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Foley & Lardner
;      STREET:  3000 K Street, N.W., Suite 500
;      CITY:  Washington
;      STATE:  D.C.
;      COUNTRY:  USA
;      ZIP:  20007-5109
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/752,929
;      FILING DATE:  20-NOV-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/375,709
;      FILING DATE:  20-JAN-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/178,251
;      FILING DATE:  14-MAY-1993
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  JP 4-147945
;      FILING DATE:  15-MAY-1992
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  WEGNER, Harold C.
;      REGISTRATION NUMBER:  25,258
;      REFERENCE/DOCKET NUMBER:  53466/150/AAOK
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (202)672-5300
;      TELEFAX:  (202)672-5399
;      TELEX:  904136
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  1983 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  DNA (genomic)
;    ORIGINAL SOURCE:
;      ORGANISM:  Shewanella putrefaciens SCRC-2874 (FERM
;      ORGANISM:  BP-1625)
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..1983
;    FEATURE:
;      NAME/KEY:  mat_peptide
;      LOCATION:  1..1983
US-08-752-929-2
```

Alignment Scores:			
Pred. No.:	0.169	Length:	1983
Score:	93.00	Matches:	75
Percent Similarity:	32.96%	Conservative:	43
Best Local Similarity:	20.95%	Mismatches:	117
Query Match:	5.25%	Indels:	123
DB:	1	Gaps:	19